

Full Title

IS DRUG DEPENDENCE A CHRONIC MEDICAL ILLNESS:

Implications for Treatment, Insurance and Outcome Evaluation

Running Title

DRUG DEPENDENCE AS A CHRONIC ILLNESS?

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ABSTRACT (220 words)

Background: We examine the evidence that drug "dependence" is a chronic medical illness - comparing its etiology, presentation, course and treatment response to three other chronic illnesses - adult onset diabetes, hypertension and asthma.

Methods: A focused literature review compared some of the defining characteristics of chronic illnesses (e.g. etiology, genetic heritability, and pathophysiology) and response to treatment (compliance and relapse) in addiction and the other chronic illnesses.

Results: Personal choice, family and environmental factors are involved in the etiology and course of all these disorders. Genetic heritability is also important and comparable across all disorders. Effective medications are now available for the treatment of nicotine, alcohol, and opiate - but not cocaine dependence. Medication compliance and relapse rates are similar across all illnesses.

Conclusion: There is reason to consider drug addiction as a chronic medical illness. Contemporary medical treatments can reliably provide cost-effective reductions in drug use, and its attendant public health problems – but not cure. Drug dependence treatments designed to discharge patients upon resolution of the acute symptoms - have not been effective. Continued, outpatient management of drug use symptoms and their sequelae with medications and brief therapies can produce enduring public health benefits comparable to those seen in other chronic illnesses. The available data suggest that drug dependence should be insured, treated and evaluated in the same manner as other chronic illnesses.

Key Words: Drug Dependence Treatment, Chronic Illness, Outcome of Treatment, Genetics of Addiction, Relapse Rates Following Treatment, Compliance with Treatment

INTRODUCTION

Many expensive and disturbing social problems in this country can be traced directly to drug dependence. For example, a recent study (1) estimated that drug dependence costs American society approximately \$67 billion each year. The National Institute on Justice reported that of the more than one million prisoners in federal institutions this year, over 60% had crimes that were connected with drug use (2). No less significant is the fact that more than three fourths of all foster children in this country are the offspring of alcohol and/or drug dependent parents. Finally, the current efforts to foster employment among those on welfare are facing substantial problems associated with alcohol and other drug dependence.

These pervasive and expensive effects of drugs on all social systems in our country have been important in shaping the public view that the “drug issue” is primarily a "social problem" requiring interdiction and law enforcement; rather than a "health problem" requiring prevention and treatment. This is a view that is apparently shared by many physicians. Few medical schools have an adequate required course in addiction. It has been repeatedly documented over the past three decades that a majority of physicians do not screen for signs of alcohol or drug dependence during routine examinations (3). Apparently there is the feeling that such screening efforts are wasted. A survey of general practice physicians and nurses indicated that none of the currently available medical or health care interventions would be ‘...appropriate or effective in treating addiction.’ (4).

This opinion appears to be supported by the fact that 40% to 60% of addicted individuals who receive treatments for alcohol or drug dependence return to active substance use within a year following treatment cessation (5). This "failure" of treatment to reliably produce a cure for drug dependence appears to confirm the suspicion that treatment is an inadequate and inappropriate response to the drug issue.

To explore this issue further we begin with the assumption that if drug dependence were an "illness" then it must be a chronic condition with a variable course and no known cure. Thus, the first part of the

paper examines the clinical presentation of drug dependence through parallels in etiology, presentation and course of illness with other well-characterized chronic illnesses such as adult onset diabetes, hypertension and asthma. These conditions were selected because they also have a variable course and while responsive to medical interventions, are not yet curable.

The second part of the paper reviews recent advances in the medical treatment of drug dependence, including the development of new medications and studies comparing treated and untreated samples. We accepted as "effective" only those treatments that produced both reduction of drug use and improved functional status, since these standards of effectiveness have been suggested for other chronic illnesses (6). We asked whether treatments for drug dependence produce results that are comparable to those seen in our three comparison illnesses. It is important to state in advance that we are aware that arguments by analogy are limited; even marked similarities across these conditions cannot prove that addiction is an illness. Nonetheless, we believe the comparative analysis of addiction with other chronic illnesses offers some instructive and provocative implications for insuring, treating and evaluating outcomes of addiction treatments.

PART I - Etiology, Course and Diagnosis of Addiction

There has been considerable debate regarding the inappropriate "medicalization" of various conditions and problems (7). The public has grown skeptical of new "syndromes" and conditions that do not appear to conform to common sense diagnostic criteria for "true" medical illnesses. For example, a New York Times editorial (8) suggests that to consider cigarette smoking a medical disorder "...shifts responsibility away from the individual... helps doctors profit," and has "...little to do with improving the public health." Many believe that "medicalization" of addiction is simply a way for physicians to declare

more territory under their jurisdiction. Much of this skepticism is understandable when the term addiction has been applied to sex, gambling, work and even chocolate.

A) Advances in Diagnosing Drug Dependence – Can the supposed pathologic state of drug “dependence” be reliably differentiated from the non-pathologic state of “drug use?” This distinction has not always been clear since most adults have “used” alcohol and/or other drugs during their lives - sometimes heavily to the point of “abuse” - but rarely to the point where it could reasonably be called an “illness.” Further compounding this difficulty has been the lack of a laboratory test for dependence or even standardized definitions for the terms “addiction” and “dependence.” The vagueness of these terms meant that diagnoses were often unreliable across different practitioners or different parts of the country. This situation changed dramatically as a result of the concept of the dependence syndrome formulated by Edwards and Gross (9) and translated operationally through the Diagnostic and Statistical Manual of Mental Disorders (DSM) (10). Now in its fourth iteration. DSM-IV defines dependence as a pathologic condition manifest by a “...compulsive desire for the drug (or drugs) despite serious adverse consequences.” Three of seven specific criteria must be satisfied for a valid diagnosis of dependence. Two of these criteria - tolerance and withdrawal - are considered evidence of neurological and behavioral adaptation to a drug. Importantly, the DSM-IV also measures whether a patient has “... reduced or eliminated previously pleasurable activities in order to concentrate on obtaining the drugs...” and/or “...used the substance instead of, or while performing important responsibilities...” (10). These seven criteria have been just as sensitive and specific as many laboratory tests used in diagnosing other illnesses. Resulting diagnoses have been shown to be reliable and valid across a range of clinical and non-clinical populations (11).

B) Genetic Factors in Drug Dependence – There have been substantial advances in understanding the genetic contribution to drug dependence over the past decade and the reader is referred to several recent review articles (See 12 - 15). One of the best methods for estimating the level of genetic contribution within all the cultural and environmental variables that are operational in familial transmission is to examine the relative rates of a disorder in monozygotic and dizygotic twins. Heritability estimates (H^2) from twin studies of hypertension range from .25 - .50 depending upon the sample and the diagnostic criteria used (16, 17). Similarly, twin studies of diabetes offer heritability estimates of approximately .80 for Type 2 (18) and .30 - .55 for Type 1 diabetes (19). Finally, twin studies of adult onset asthma have produced a somewhat broader range of heritability estimates, ranging from .36 to .70 (20, 21).

In the addiction field, several twin studies have been published recently, all showing significantly higher rates of alcoholism and/or drug dependence among twins than among siblings; and higher rates among monozygotic than dizygotic twin pairs (12 - 15). A recent twin study of heroin dependence produced a heritability estimate of .34 among males (12). Similar studies of alcohol dependence have produced heritability estimates of .55 to .65 among males (see 13 - 15). Though there is need for more studies of heritability by drug and by gender, the evidence accumulated over the past several years suggests significant genetic contribution to the risk of addiction in approximately the same range as for chronic illnesses such as asthma and hypertension.

C) Factors Associated with the Onset and Course of Illness - Since the use of alcohol and drugs is, at least initially, a voluntary action, behavioral control or "will power" is obviously a very important factor in the onset of addiction. Thus, at some level, and particularly in the case of dependence on illegal substances, the addicted individual is at fault for initiating the behaviors that lead to the dependence

disorder. Doesn't this voluntary initiation of the "disease process" set drug dependence apart, etiologically, from other medical illnesses?

In fact, there are many illness where voluntary choice contributes significantly to initiate and sustain a disease process - especially when these voluntary behaviors interact with genetic and cultural factors. For example, there is clear evidence among males, that "salt sensitivity" is a genetically transmitted (heritability estimate .74) risk factor for the eventual development of one form of hypertension (-22, 23). However, not all of those who inherit salt sensitivity go on to develop hypertension. This is because the use of salt is much more likely to be determined by familial salt use patterns, cultural factors and individual choice. Similarly, factors such as obesity, stress level, and exercise are the joint product of familial, cultural, environmental and personal choice factors (-22, 23). Thus, even among those with demonstrated genetic heritability a significant part of the total risk for developing hypertension can be traced to individual behavioral factors.

There are also involuntary components embedded within seemingly volitional choice. For example, although the choice to try a drug the first time appears to be completely voluntary, it can be influenced by uncontrolled economic and ecological factors such as availability. In addition, the effects of the initial drug use are also influenced by genetic heritability and in turn are likely to modify the course of continued use in an involuntary manner. Those whose initial physiological responses to alcohol or other drugs are extremely pleasurable will be more likely to repeat the drug-taking, than those whose involuntary, physiological reaction is neutral or even negative. Work by Schuckit and colleagues with sons of alcohol dependent fathers has shown that these sons are born with more tolerance to alcohol's effects than sons of non alcohol dependent fathers. This enhanced tolerance effect is highly influenced by direct genetic transmission (H^2 is .67) (24, 25). An example of inherited "super-sensitivity" to alcohol has been shown in a large proportion of Chinese and Japanese individuals who experience an involuntary skin "flushing" response to alcohol. This effect has been traced to the presence of an aldehyde dehydrogenase gene that controls a central part

of alcohol metabolism (–26 - 28). Individuals who are homozygous for this allele (approximately 35% of Asian population, 20% of Jewish males in Israel) have an especially unpleasant reaction to alcohol to the point where there are virtually no alcoholics found with this genotype (26 - 28).

D) Pathophysiology Associated with Drug Dependence - Are there predictable pathophysiological changes associated with the course of drug dependence; and are these changes similar to those seen in the course of other medical illnesses? The acute effects of alcohol and many other drugs have been well characterized for many years. But even a complete understanding of these acute effects cannot explain how repeated doses of alcohol and other drugs produce paradoxically increasing tolerance to the effects of those drugs concurrent with decreasing volitional ability to forego the drug. As suggested by Koob and Bloom (29), the challenge is to find an internally consistent sequence by which molecular events modify cellular events, and in turn produce profound and lasting changes in cognitions, motivation and behavior.

Research in the neurochemical, neuroendocrine and cellular changes associated with drug dependence has led to volumes of remarkable findings over the past decade. These advances have been summarized in recent special issues of *Science* and *Lancet* and in two volumes produced by the Institute of Medicine of the National Academy of Sciences (30 -, 33). Here we summarize just three areas of investigation that have produced clinically relevant information leading to medications to treat drug dependence (See below).

There is now clear evidence that most addictive drugs have well specified effects on the brain circuitry involved in the control of motivated and learned behaviors. This evidence originated from studies in animals, and using brain imaging techniques, has been confirmed in humans (30 - 34). Anatomically, the brain circuitry principally involved in most of the actions of the major addictive drugs is the ventral tegmental

area connecting the limbic cortex through the midbrain, to the nucleus accumbens (35, 36).

Neurochemically, all of the major drugs of abuse (alcohol, opiates, cocaine, nicotine) have significant effects on the dopamine system - although through different mechanisms. For example, cocaine increases synaptic dopamine by blocking re-uptake into the pre-synaptic neuron; amphetamine produces increased presynaptic release of dopamine, while opiates and alcohol disinhibit dopamine neurons thereby producing increased firing rates (-30 - 33). Opiates and alcohol also have a direct effect on the endogenous opioid system (-30 - 33). Evidence is also emerging that the GABA system plays a central role in alcohol dependence. Finally, recent work on the stress response system suggests the possibility that lasting changes in neurochemical and neuroendocrine function may occur with the development of cocaine and/or opiate dependence (37, 38).

Significantly, the ventral tegmental area and the dopamine system have been associated with the feelings of euphoria produced by naturally occurring reinforcers (29, 34). For example, animals that receive mild electrical stimulation of the dopamine system contingent upon a lever press response, will rapidly learn to press that lever tens of thousands of times, ignoring normal needs for water, food or rest, in order to maintain the stimulation of that system (34). Cocaine, opiates and several other dependence producing drugs to stimulate this reward circuitry in a supranormal manner (29 - 34). Given this basic description of the fundamental neuroanatomy and neuropharmacology of this system, it is possible to understand how addictive drugs can produce immediate and profound desire for their readministration. What is less clear is why simply preventing the administration of these drugs for some period of time would not correct the situation, set the system back to normal and, like the child who burned his fingers, lead to a "sadder but wiser" individual who would be less (instead of more) likely to readminister those drugs.

The most direct answer is that use of a drug at some dose, frequency and chronicity will reliably produce enduring and possibly permanent pathophysiological changes in the reward circuitry (37 - 39), in the normal levels of many neurochemicals (–35, 40) and in the stress response system (37, 38). It is not clear, just how much drug use is required to create these changes, how enduring the various effects are, or whether these effects will ever return to normal. Somatic signs of withdrawal generally last several days, motivational aspects of withdrawal and cognitive impairment may last several months (33) and the learned aspects of tolerance to the drug may never return to normal (35, 36, 41). For example, Volkow found impairments in the dopamine system (reduced D2 binding) of abstinent former cocaine users for as long as three months after their last cocaine use (40). In addition, her research team found reduced glucose metabolism in dopamine projection areas during cocaine abstinence and the degree of metabolism reduction correlated with the long-term reductions in radioligand binding (35). Another human imaging study found decreased uptake of radiolabeled DOPA into the striatum of cocaine users tested one week after their last cocaine dose, indicating decreased dopamine synthesis at this early time point (35). Still other studies have documented areas of poor cortical blood flow ("patchy defects") and reduced prefrontal metabolism in abstinent cocaine abusers (42, 43). Work investigating the stress response system suggests sustained changes in the stress response system following the development of opiate or cocaine dependence (37, 38). Taken together, these studies suggest that the neurochemical and possibly the neuroendocrine systems of abstinent but formerly drug dependent patients, are functioning irregularly and at a reduced level for a very long time.

A second explanation for the enduring pathology seen among drug dependent persons and their tendency to become re-addicted lies in the integration of the reward circuitry with the motivational, emotional and memory centers that are co-located within the limbic system. Connections among these "survival circuits" are apparently designed to give prominence and emotional significance to the normal

biological events that usually precede arousal of those circuits (food, danger, sex). These circuits are also intimately involved in the control of emotion, motivation and "biologically significant memories" (34, 39). Importantly, these interconnected regions allow the organism not only to experience the pleasure of rewards, but also to learn the signals for them and to respond in an anticipatory manner.

This pairing of a person (drug using friend), place (corner bar), thing (paycheck), or even an emotional state (anger, depression) with drug use, with its supranormal activation of the reward circuits, leads to rapid and entrenched learning or "conditioning." Cues paired with drug use acquire some of the properties of the drug itself. Thus, previously drug dependent individuals who have been abstinent for even long periods, may encounter a person, place or thing that has been previously associated with their drug use, producing significant physiological reactions. In the case of cocaine, these reactions include palpitations and other signs of sympathetic arousal such as ear-ringing, chest-tightness, light-headedness, a "cocaine taste" in the back of the throat (41). In the case of heroin, this reaction includes pilo-erection, stomach cramps, fever and withdrawal-like symptoms (44). Importantly, and regardless of the particular drug, these responses are usually accompanied by profound desire or craving for that drug (41, 43, 44). Ingrained through learning, the confluence of the physiological, emotional and craving symptoms combine to produce the "loss of control" that has been considered the hallmark of drug dependence (10).

While these conditioned physiological responses have most recently been studied in cocaine dependent individuals, they were first shown more than twenty years ago in opiate dependent (See 44) and in alcohol dependent (45) individuals. For example, Childress, O'Brien and their colleagues have shown the profound neurostimulation effects of cues that had been previously associated with use of drugs - even among stably abstinent former users (41). Using positron emission tomography (PET) they compared regional cerebral blood flow in limbic and control brain regions of 14 detoxified male cocaine users and 6 cocaine-naïve controls during exposure to neutral videos and to videos of cocaine-related scenes. During

the cocaine video, formerly cocaine dependent subjects experienced increased craving and showed a pattern of limbic (amygdala and anterior cingulate) increases and basal ganglia decreases in regional cerebral blood flow. This pattern did not occur in cocaine-naïve controls, nor among the formerly cocaine dependent patients in response to the neutral video (41). These findings indicate that even artificial video scenes of cocaine-related stimuli, presented in the sterile and remote context of a PET laboratory, produced excitation of brain reward regions that mimicked the effects of the drug itself.

It is likely that both the direct physiological changes produced by the drugs themselves and the acquired effects produced by conditioned cues are involved in the ultimate explanation of the continued vulnerability to relapse among even motivated, abstinent, formerly drug dependent individuals (See 37). At the same time, there is much left to explain. As Childress has noted (41), most people have had their reward circuitry associated with natural reinforcers such as food, sex, sleep, and even some drug or alcohol use. Why don't all people use natural rewards compulsively? What distinguishes those who use alcohol and other drugs but do not become addicted, from those who use similar amounts or at similar frequencies but do become dependent? The data suggest that genetic heritability, environmental availability, cultural acceptance and learned factors are all involved in the explanations – but no definitive answers are yet possible.

PART II - Does Drug Dependence Respond to Treatments?

Regardless of the etiology, pathophysiology or course of addictive disorders, the question of most import is whether these conditions will actually respond to medications and/or other forms of medical treatment. There is a large and still growing literature on addiction treatment outcomes (See 31 - 33, 46 - 48). Here we present only a few examples from that literature that address questions of particular import to physicians.

A) Do Treated Patients Show Better Outcomes Than Untreated Patients? While it is not ethically possible to deny available treatment to those whose condition appears to require it, there are situations where treatments have not been applied to substance dependent persons. These situations offer some indication of the course of addiction in the absence of treatment. Intravenous Drug Users - Metzger et al. (49) examined the drug use, needle sharing practices and HIV infection rates of two large samples of opiate addicted patients in the Philadelphia area. The "In-Treatment" (IT) group was comprised of 152 patients randomly selected at admission to a community methadone maintenance program. "Out of Treatment" subjects (OT) were referred to the study by IT subjects. These too were heroin using individuals matched to the IT group on age, race, gender, neighborhood and other relevant background factors associated with drug use. However, these 103 OT subjects had not had any form of addiction treatment for at least one year.

Both groups of patients were interviewed and tested for HIV status every six months over the next seven years (90% contact rates at each interview). At the initial assessment point, 13% of the IT sample and 21% of the OT sample tested positive for HIV infection. By the seven year point, 51% of the OT group, but only 21% of the IT group tested HIV positive (69). Hence, treatment was associated with a 60% reduction in the odds of becoming HIV infected.

It should be clear that while the between-group difference in conversion rate was substantial, this is not proof that treatment participation was the causal agent. It is likely that the Out of Treatment subjects lacked the motivation for treatment found among the treated subjects, and this lack of desire for personal change, rather than the effects of the treatment itself, could have produced the status differences seen.

Motivated but Untreated Patients – A recent study of cocaine dependent individuals who applied for – but were denied treatment - helps to shed light on the role of motivation. In this four-week study

of waiting list patients by Urschel and his colleagues (46), sixty-eight cocaine dependent individuals were contacted at the time of their application for inpatient treatment. Due to the unavailability of beds, these individuals were put on a waiting list for treatment.

Results indicated that over the ensuing four weeks, only 16% of the group received any treatment services from other sources (typically detoxification and/or temporary housing at a community shelter). Only this small subgroup showed reductions in their alcohol and other drug use, but no improvements in their health and social function. Among those who received no treatment services, 57% reported increased severity of medical problems and 81% reported worse employment and support problems over the four-week waiting period. These data indicate that the drug use and the related health problems showed little improvement without treatment, despite their initial motivation for change.

Unmotivated Individuals – Another way to separate the effects of drug dependence treatment from the effects of motivation is to compare treated and untreated substance dependent individuals who were explicitly not interested in treatment. Such a study was recently performed by Booth and associates (50) among 4,000 intravenous drug users seeking HIV testing and AIDS services as part of a multi-site AIDS initiative in fifteen cities. In each city, injection drug users were offered an opportunity to participate in drug abuse treatment as a part of AIDS risk reduction services. In all cities, subjects were randomly assigned to either a standard HIV counseling and testing intervention or to an enhanced intervention consisting of the standard intervention plus three sessions of motivational counseling from a health educator. At six-month follow-up, those who were randomly assigned to the enhanced intervention showed half the rate of drug injection (20% vs. 45%), four times the rate of abstinence (confirmed by urinalysis) and significantly lower arrest rates (14% vs. 24%) than those randomly assigned to receive just HIV counseling and testing (50).

This finding suggests that treatment entry is not simply a matter of pre-conceived desire for change that would have occurred anyway - or the rates of treatment entry among these randomly assigned groups would have been approximately equal. Studies of other illnesses show that screening and brief advice from physicians can affect the "motivation for treatment" among patients and the longer term course of their health. The Booth et al. data suggest this is true even for seriously and chronically addicted individuals.

The Costs of Untreated Addiction in Pregnancy. A study of drug abuse treatment among pregnant, substance dependent women was performed by Svikis et al. (51). The dangers of drug use during pregnancy are extreme, for the mother and the child. Moreover, the costs associated with even the acute care of neonates born to addicted women can be extreme (52). Accordingly, the Svikis et al. study was designed to test the effects of standard drug dependence treatment delivered in the context of peri-natal care, on the health status and costs of care for the mothers and their children. As in the Booth et al. study, the effects of drug abuse treatment were assessed among individuals who did not originally apply for treatment. All pregnant women in the study had simply applied for pre-natal care services and were found cocaine-positive on a routine drug screen. Two groups were compared: the first 100 pregnant women admitted to the combined drug dependence treatment-plus-peri-natal care program and 46 comparison women, drawn from the same screening process, and matched for race, mental status, insurance coverage and parity with the treated women, but who had been identified during the year prior to the opening of the experimental treatment program. Drug dependence treatment consisted of one week of residential care focused on stabilizing the women and engendering commitment for continued treatment. This treatment was followed by twice-weekly addiction counseling in the context of the scheduled prenatal visits.

Results At the time of delivery indicated that 37% of the treated patients used cocaine (by urine screen) as compared with 63% of the untreated women. Babies of the treated women averaged higher birthweights (2934 gms. vs. 2539 gms.) and longer gestational periods (39 wks. vs. 34 wks.) than those of

the comparison group. Following the deliveries, 10% of the babies in the treated group required treatment in the neonatal intensive care unit (average length of stay of 7 days). In comparison, 26% of the babies in the untreated group required intensive care (average length of stay of 39 days). The total costs of care (including drug abuse treatment) for the mother and the baby in the treated group averaged approximately \$14,500; much lower than the average of \$46,700 for the pre-natal care – only group.

These calculations are quite conservative since they did not include costs of criminal and family court, child and family services or continued health care for mother and child. Nonetheless, the data present evidence that drug dependence treatment can be cost effective in this severely affected population. The data also suggest that drug dependence treatment can be combined effectively with traditional perinatal medical care.

B) Are Drug Dependence Disorders Responsive to Medications - If physicians are expected to play a role in the treatment of drug dependence, it is reasonable to ask whether there are effective medications available. Several anti-addiction medications have been developed under FDA guidelines, researched in randomized clinical trials and many have now reached the over-the-counter market. Perhaps the best known and studied of these medications are nicotine gum and patch and bupropion (Zyban®) used in the treatment of smoking cessation. These medications plus an educated physician force have made an important contribution in the larger public health efforts to reduce cigarette consumption.

A review of the progress in treating alcohol, cocaine and opiate addiction suggests that medications for these problems have been developing more slowly, due in part to the lack of a large commercial market. However, the identification, development and testing of new drugs for the treatment of these disorders, has

advanced substantially over the past several years, as reviewed in a recent Institute of Medicine publication (see 33).

Opioid Addiction - Agonists, partial agonists and antagonists are the three primary types of medications available for the treatment of opioid dependence. All of these medications act directly upon the opioid receptors, particularly mu-receptors (–32, 33). Agonist medications such as methadone are prescribed acutely as part of an opioid detoxification protocol, or chronically in a maintenance regimen. The long acting form of methadone (48 - 72 hour duration), Levo Alpha Acetyl Methadol (LAAM) has recently received FDA approval and has been accepted by 16 states for prescription, but only at methadone maintenance programs. Double blind, placebo controlled trials have shown methadone to be effective in detoxifying opiate dependent patients in both inpatient and outpatient settings, although the effects of detoxification alone, without continuing treatment, have been uniformly poor (–53, 54). As a maintenance medication, numerous controlled trials have shown that methadone's oral route of administration, slow onset of action and long half life have been very effective in reducing opiate use, crime and the spread of infectious diseases, as was recently validated by a panel of impartial physicians and scientists in a National Institutes of Health consensus conference 55).

Partial agonist medications such as buprenorphine have also been developed over the past several years (56). Buprenorphine is administered sub-lingually and is active for approximately 24 - 36 hours. Like methadone, buprenorphine significantly reduces craving for opiates. Large scale, double-blind, placebo controlled trials with buprenorphine have shown reductions in opiate use that are comparable to those seen with methadone (56). The partial agonist actions of buprenorphine may have some advantages over methadone since it produces few withdrawal symptoms upon discontinuation of its use (56). The

combination of buprenorphine with naloxone (Suboxene[®]) is presently undergoing testing for prescription in general practice settings (56).

Opioid receptor antagonists such as naltrexone have also been used for more than 25 years in the treatment of opiate dependence (See 57). Naltrexone is an orally administered opiate antagonist that blocks actions of externally administered opiates such as heroin through competitive binding for 48 to 72 hours. Like methadone and buprenorphine, naltrexone is a maintenance medication, designed as an "insurance policy" in situations where the patient will be confronted with relapse situations. Opiate antagonists produce neither euphoria nor dysphoria when prescribed to abstinent opiate addicts, but compliance has been generally poor with most field studies showing one-month retention rates of less than 25%. For this reason, several studies have combined naltrexone with social or criminal justice sanctions to increase adherence and sustain the benefits from the medication. For example, naltrexone is routinely used in the monitored treatment of physicians, lawyers, nurses and other professionals (58) where maintaining a license to practice is contingent upon maintaining abstinence. In a recent controlled trial with opiate dependent federal probationers, Cornish and colleagues showed that naltrexone added to standard probation produced 70% less opiate use and 50% less re-incarceration rates than standard probation alone (59).

Antagonist Medications in the treatment of Alcohol Dependence - Naltrexone (marketed under the trade name - Revia[®]) has also been found to be effective in the treatment of alcohol dependence (60, 61). Naltrexone at 50 mg./day has been approved by the FDA as a safe, effective pharmacological adjunct for reducing drinking among alcohol dependent patients. Its mechanism of action appears to be the blocking of at least some of the "high" produced by alcohol's effects on mu opiate receptors.

More recently, European researchers have found encouraging results using acamprosate to block craving and return to alcohol abuse. While acamprosate acts on different receptor systems than naltrexone,

the clinical results are remarkably similar (62). Alcohol dependent patients prescribed acamprosate showed 30% greater abstinence rates at six month follow-up than those randomly assigned to placebo. Further, those who returned to drinking while receiving acamprosate reported less heavy drinking (five or more drinks) than those receiving placebo (62).

Medications in the Treatment of Cocaine Dependence - While there are now several effective behavioral treatments developed for the treatment of cocaine dependence (see 31 - 33, 46 - 48) there is not yet a safe and effective medication (for recent review see 33). Research continues in this important area and there are indications of a potentially successful vaccine that can immediately bind to, and thereby inactivate active metabolites of cocaine (See 63). This promising work is currently being tested in animal models but clinical trials will not be scheduled for several years.

In summary, there are medications currently available for use by physicians in the treatment of nicotine, alcohol, and opioid dependence. These medications have been tested in multiple trials and have been shown effective. Their use is increasing as more substance dependence is treated by primary care physicians (64). At the same time, there are still relatively few patients who receive, or practitioners who prescribe these medications. As in the treatment of other medical illnesses, managed care companies have been slow to approve new addiction medications (65).

C) Are the Treatments for Drug Dependence Comparable in Effectiveness to Treatments for Other Chronic Diseases? There is no reliable "cure" for drug dependence. For the reasons outlined above, those dependent upon alcohol and/or other drugs who attempt to continue but reduce their use are likely to have problems in maintaining "controlled use." Among those who become addicted, patients who comply with the recommended regimen of education, counseling and medication have favorable outcomes during and for at least six to twelve months following treatment (-46 - 48). However, most of those who

start any type of addiction treatment drop out prior to completion, or they ignore physician advice to remain on medications and to continue participation in aftercare or AA. Problems of low socioeconomic status, co-morbid psychiatric conditions and lack of family/social supports are among the most important predictors of poor adherence during addiction treatment, and of relapse following treatment (46 – 48, 66, 67).

One-year follow-up studies have typically shown that only about 40 - 60% of treated patients are continuously abstinent: although an additional 15 - 30% have not resumed dependent use during this period (46 – 48, 66, 67).

It is quite discouraging to many in the addiction treatment field that so many drug and alcohol dependent patients fail to adhere to the recommended course of treatment and that so many subsequently resume substance use. As indicated above, there are now several medications that have demonstrated effectiveness in the treatment of nicotine, alcohol and opiate dependence. For these medications to be effective, they must be taken on a regular basis, but lack of patient adherence has severely limited their impact (55 - 64). Ongoing clinical research in this area is focused upon the development of longer acting or depot forms of these medications, as well as behavioral strategies to increase patient compliance (63).

As suggested previously, hypertension, diabetes and asthma are also chronic disorders, requiring continuing care throughout a patient's life. At the same time, these disorders are not necessarily unremitting or unalterably lethal, as long as the treatment regimen of medication, diet and behavioral change are followed. This last point requires elaboration. Treatments for these medical disorders are heavily dependent upon behavioral change and medication compliance to achieve their potential effectiveness. In turn, there have been numerous strategies developed to retain these patients in care and to encourage medication adherence and behavioral change.

In reviews of treatment outcome studies in adult-onset hypertension, diabetes and asthma, patient adherence to the recommended medical regimen was the most significant determinant of treatment outcome (68). Unfortunately, these studies have shown less than 60% of Type 2, insulin dependent, adult diabetics fully comply with their medication schedule (e.g. 69), and less than 40% of hypertensive or asthmatic patients adhere fully to their medication regimens (e.g. 69, 70). The problem is even worse for the behavioral and diet changes that are so important for the maintenance of gains in these chronic illnesses. Again, studies indicate that less than 30% of adult onset asthma, hypertension or diabetes patients comply with prescribed diet and/or behavioral changes that are designed to increase functional status and to reduce risk factors for reoccurrence of the disorders (e.g. 70 - 72). Across all three of these chronic medical illnesses, compliance, and ultimately outcome, is poorest among patients with low socioeconomic status, low family and social supports or significant psychiatric co-morbidity (69 - 72).

This review of medication and behavioral compliance in the treatment of other chronic medical illnesses suggests important parallels with the treatment of drug dependence. In all these disorders, lack of patient adherence to the treatment regimen is a major contributor to the reoccurrence of symptoms; and in all these illnesses adherence is poorest among those with co-morbid medical, psychiatric, family and social problems. Perhaps because of these similarities in treatment adherence there are also similar relapse or reoccurrence rates across all these disorders. Outcome studies indicate that 30 - 50% of adult, insulin-dependent, diabetic patients, and approximately 50 - 70% of adult hypertensive and asthmatic patients suffer reoccurrences of their symptoms each year to the point that they require some form of additional medical care to re-establish symptom remission (73 - 76). Many of these reoccurrences result in serious health complications. For example, limb amputations and blindness are common results of treatment non compliance among diabetics (69, 73, 77). Stroke and cardiac disease are common problems associated with exacerbation of hypertension (70, 76, 78).

DISCUSSION AND IMPLICATIONS

Few of those who try drugs or even use drugs regularly, become “drug dependent.” Although science has made great progress over the past several years, we cannot yet fully account for the physiological and psychological processes that transform controlled, voluntary use of alcohol and/or other drugs into uncontrolled, involuntary dependence on these substances. However, twin studies indicate a definite role for genetic heritability in alcohol and drug dependence. Neuropharmacological and neuroimaging research indicate that there is a predictable physiological course to dependence. Finally, research in nosology indicates that dependence can be reliably and validly differentiated from even heavy drug “use.” In summary, evidence from the first part of the review indicated that drug dependence was generally similar to the three comparison conditions in terms of heritability, onset and clinical course.

However, arguments by analogy are limited. Even if there are elements of similarity between drug dependence and these three chronic illnesses, this comparison is not a basis from which to argue that addiction is an “illness” nor that medical treatments would be effective in reducing addiction. Thus in the second part of the review we examined evidence for the effectiveness of medications and medically oriented treatments for addiction. There are now many controlled studies of addiction treatments. The few examples exemplified the broader literature, showing evidence of significant reductions in drug use, improved personal health and significant cost offset (see 31, 33, 46 - 51). We also found evidence for potent and well tolerated medications for the treatment of nicotine, alcohol, and opiate (33, 55) - but not cocaine dependence (63).

Finally, as is the case in treatments for other chronic disorders, we found major problems of compliance during treatment and relapse following treatment among addicted patients. In fact, the same

patient problems of poverty, low family support and psychiatric co-morbidity were predictive of non-compliance and relapse across all of these disorders (See 66, 69 – 71, 75).

Of course there are differences between addiction and the selected comparison illnesses. Unlike any other chronic illness, drug dependence results from illegal behavior. In addition, while behavioral changes in diet and lifestyle can reverse the early course of some forms of asthma, hypertension and diabetes, there is a later point in these illnesses where behavioral change alone is not sufficient for symptom remission and medications are required. In contrast, work by Vaillant and others has shown that some, even chronically addicted individuals can achieve almost full symptom remission without medical treatment, by eliminating alcohol and changing their lifestyle (79, 80). At the same time, few chronically addicted individuals achieve stable symptom remission without treatment.

Our review suggests that drug dependence – but not drug “use” - shares many of the features common to other chronic illnesses. Prior to discussing the implications of this suggestion, it is important to restate that we are well aware that even the numerous similarities discussed here are not adequate to prove addiction is an illness. At the same time, the noted similarities in onset, course and particularly, response to treatment raise the question why medically oriented treatments are seen to be appropriate and effective when applied to asthma, diabetes and hypertension – but seemingly inappropriate and ineffective when applied to alcohol and drug dependence. We think the discrepancy in perception is because contemporary addiction is not treated, insured or evaluated like other chronic illnesses. Again, a comparison of current treatment strategies is an appropriate illustration.

Contemporary treatment for drug dependence typically consists of an admission to a 30 to 90-day outpatient, specialty treatment program. Few of these programs provide medical monitoring or medication, concentrating instead on counseling and behavioral change strategies. The goal of these contemporary treatment programs has been to rehabilitate addicted patients and discharge them, as one might rehabilitate a

surgical patient following a joint replacement. Outcome evaluations are typically conducted six to twelve months following treatment discharge. A major (sometimes the exclusive) outcome in all these evaluations is whether the patient has been continuously abstinent after leaving treatment.

Consider a “rehabilitation” strategy applied to hypertension. Patients who meet diagnostic criteria for hypertension would be admitted to a 30 - 90 day outpatient specialty “hypertension rehabilitation program” where they would receive medication, behavioral change therapy, dietary education, and an exercise regimen. Because of insurance limits and the rehabilitation-oriented goals, the medication would be tapered during the last days of the treatment and the patients would be referred to community sources. An evaluation team would re-contact patients six months later and determine whether they had been continuously normotensive throughout that post treatment period. Only those patients that met this criterion would be considered “successfully treated” under this set of evaluation expectations.

We see three sets of implications that derive from this line of argument. For primary care physicians, this review suggests that addiction should be included as part of the regular medical school and residency curricula. Further, there should be efforts to adapt medical monitoring strategies presently used in the treatment of other chronic illnesses - to the treatment of addiction. Indeed, these types of strategies have already been initiated with some success (64). Research is needed to help both physicians and patients determine when to change from a “rehabilitation” strategy, in which the major goal is to help the patient leave treatment; to a chronic care strategy, in which the major goal is to help the patient accept and comply with ongoing treatment. It is an open question whether a rehabilitation strategy delivered in a specialty program, or a chronic care, disease management strategy coordinated through primary care, will provide the maximal benefits for addicted patients and to society.

For insurers, employers and those in health policy, our review offers support for recent initiatives to include addiction as part of insurance “parity” legislation. Like other chronic illnesses, it is clear that the

effects of addiction treatment are optimized when patients remain in continuing care and monitoring. Thus, it may be appropriate to provide health benefits (even incentives) for continued outpatient, medication and behavioral management visits – without current limits or restrictions on the number of days or visits covered. It is likely that a chronic care, disease management approach to addiction would increase treatment initiation and engagement by reducing the stigma and alienation of segregated treatment. It is unknown whether an expanded insurance benefit of this type would reduce long term costs associated with the later stages of addiction – or merely increase utilization with no clear cost offset.

For clinical and evaluation researchers, this review suggests the importance of appropriate methods and reasonable standards in the evaluation of addiction treatments. It is likely that the standard “pre – post” treatment evaluation designs have underestimated the effects of addiction treatments by essentially ignoring the “during treatment” period and focusing instead on the post treatment period (See 46). As illustrated in the above example, such a design would be completely inappropriate for evaluations of hypertension, asthma or diabetes treatments. In this regard, it is interesting that the high relapse rates among diabetic, hypertensive and asthmatic patients following cessation of their medications have been considered evidence of the effectiveness of those medications, the need to retain patients in medical monitoring and the need for compliance enhancement strategies. In contrast, relapse to drug or alcohol use following discharge from addiction treatment has been considered evidence of treatment failure.

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